Remarks

I. Status of the Claims

Reconsideration of this Application is respectfully requested.

Upon entry of the foregoing amendment, claims 8-10, 12-15, 17, 25, 27, and 30-38 are pending in the application, with claims 8, 10, 13, 25, 30, and 34 being the independent claims. Claims 1-7, 11, 16, 18-24, 26, and 28-29 are sought to be cancelled without prejudice to or disclaimer of the subject matter therein. Applicant reserves the right to prosecute the canceled subject matter in related applications. New claims 30-38 are sought to be added. Support for the new claims may be found throughout the specification as originally filed, either inherently or explicitly. Specifically, support for the new claims can be found in the specification at paragraph 0114, pages 24-25; paragraph 0015, pages 3-4; paragraphs 0091-0092, pages 19-20; paragraph 0098, pages 20-21; paragraph 0107, pages 22-23; paragraph 0193, page 43; paragraph 0130, pages 28-29; paragraph 0147, pages 32-22; and Example 2. These changes are believed to introduce no new matter, and their entry is respectfully requested.

Based on the above amendment and the following remarks, Applicant respectfully requests that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

II. Objections to the Specification

In section 2 of the Office Action at page 2, the Examiner has objected to the specification for failure to comply with the requirement of 37 C.F.R. § 1.821(d). As requested by the Examiner, the specification has been amended to indicate the SEQ ID

NO for the oligonucleotide primers in paragraphs 0211 and 0212. Hence, this objection is rendered moot.

In section 3 of the Office Action at page 2, the Examiner has objected to the disclosure for a typographical error. As requested by the Examiner, the specification has been amended to correct the typographical error. Hence, this objection is rendered moot.

III. The Rejections Under 35 U.S.C. § 112, First Paragraph

A. The Enablement Rejection Of Claims 1-12 and 16-29

In section 5 of the Office Action at page 2, the Examiner has rejected claims 1-12 and 16-29 under 35 U.S.C. § 112, first paragraph as allegedly containing subject matter which was not described in the specification in such as way as to "enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims." Office Action at page 3. Applicant respectfully disagrees with this rejection. However, to expedite prosecution of the present application and not in acquiescence to this rejection, claims 1-7, 11, 16, 18-24, 26, and 28-29, as well as subparts (c)-(f), and (h) of claim 25 have been cancelled without prejudice or disclaimer, thus rendering moot the portion of this rejection that applied to these claims. Applicant respectfully traverses this rejection, as it may be applied to the remaining claims.

The test for enablement is whether the disclosure when filed contained sufficient information regarding the subject matter of the claims as to enable one skilled in the pertinent art to make and use the claimed invention. M.P.E.P. § 2164.01. The standard applied is whether the experimentation needed to practice the invention is undue. *In re Wands*, 858 F.2d 731, 737, 8 U.S.P.Q.2d 1400, 1404 (Fed. Cir. 1988). However, "[a]

patent need not disclose what is well known in the art." *Id.* Whether the specification is enabling must be analyzed in light of factors such as the state of the prior art and the level of one of ordinary skill. *Id.*; *see also* M.P.E.P. § 2164.01(a).

With regard to claims 8-9, the Examiner has alleged that the claims are not enabled because "the term 'comprising' is open-ended. . . . Given the indefinite number of undisclosed purified protein, it is unpredictable which undisclosed proteins mentioned above bind to any antibody that binds to the polypeptide of SEQ ID NO:2 or induce apoptosis. . ." Office Action at page 5. Applicant respectfully disagrees with this rejection, but to expedite prosecution of the application, and not in acquiescence to this rejection, Applicant has amended the claims to recite "consisting of at least" to clearly indicate that the claimed purified proteins are portions of SEQ ID NO:2, including full length SEQ ID NO:2.

With regard to claim 10, the Examiner has alleged that the claim is not enabled because "the term 'comprising' is open-ended. . . . Given the indefinite number of undisclosed purified protein, it is unpredictable which undisclosed proteins mentioned above bind to any antibody that binds to the polypeptide of SEQ ID NO:2 or induce apoptosis. . ." Office Action at page 5. Applicant respectfully disagrees with this rejection, but to expedite prosecution of the application, and not in acquiescence to this rejection, Applicant has amended the claim to recite "consisting of." Applicant respectfully traverses the rejection as it may be applied to claim 10 as amended.

First, Applicant respectfully asserts that it would not have required undue experimentation for one of ordinary skill in the art to generate a fragment of amino acids 1-281 of SEQ ID NO:2 which induces apoptosis. The AIM-I polypeptide is a member of the TNF-ligand superfamily, a well-characterized family of proteins. As discussed at

pages 1-2 of the specification, TNF family ligands have a well-characterized and distinctive structural topology that is found in all members of the family. Furthermore, Applicant asserts that the structural topology of TNF family ligands was very well known in the art when the present application was filed. *See, e.g.*, Gruss and Dower, *Blood 85*:3378-3404 (1995), which was incorporated by reference in the present application (Specification at paragraph 0005, pages 1-2). A copy of this article is attached hereto as Exhibit A.

One of skill in the art would know how to make fragments of SEQ ID NO:2 that retain the apoptotic function of AIM-I. The present application has provided guidance about the fragments of the polypeptide that still retain the structural or functional attributes of AIM-I. Specifically, the specification states that:

> Highly preferred . . . are fragments that contain regions that are homologs in sequence, or in position, or in both sequence and [position] to active regions of related polypeptides, such as the related polypeptides set out in Figure 2, which include members of the TNF family.

See specification at paragraph 0115, page 25.

It was well known in the art that there was a characteristic pattern of sequence conservation in the TNF family ligands which could be used by one of skill in the art to routinely predict and determine which amino acid fragments of AIM-I could be selected and still retain the structural or functional attributes of AIM-I. *See* Gruss and Dower page 3380 and Figure 2. Specifically, this reference shows that there was a detailed understanding of where the activity of the TNF family ligands was located and what minimum portion of the protein was required for the TNF family ligands to be active.

> [S]equence alignments show that as with the receptors, there is a characteristic pattern of sequence conservation, there being 9 short regions of conserved sequence

> distributed along the length of the molecules (Fig. 2). Superposition of the sequences on the three dimensional structures of TNF and LTα shows that these regions correspond to the strands that form the core of the protein.

Id. at 3380. By routinely superimposing the amino acid sequences of the TNF ligand superfamily members on the three dimensional structure of TNF, one of ordinary skill in the art would know what amino acids of the protein were required to retain the function and activity of the protein.

Thus, given that AIM-I is a member of the TNF-ligand superfamily, one of ordinary skill in the art would have been able to predict and determine which amino acids of AIM-I were required to retain its apoptotic function, and could then make polypeptides having those amino acids. At that point, one of ordinary skill in the art would easily have been able to test polypeptides of the invention for apoptotic activity using routine techniques. *See, e.g.*, Suda *et al.*, *Cell 75*, 1169-1178 (1993) (Attached hereto as Exhibit B). *See also* Exhibit A page 3382. Accordingly, on the basis of the specification and knowledge in the art regarding proteins in general and TNF ligands in particular, one of ordinary skill in the art would have reasonably been able to predict, and routinely make and test, a purified protein consisting of a fragment of amino acids 1-281 of SEQ ID NO:2 that induced apoptosis of a cell line derived from pathologic tissue, or induced apoptosis of T cells, without undue experimentation.

Second, based on the specification, one of ordinary skill in the art would have known how to use the claimed purified proteins to produce antibodies specific for the polypeptide of SEQ ID NO:2. The present specification clearly discloses how to produce and test antibodies for their ability to bind to the AIM-I polypeptide and fragments thereof. *See* specification at paragraphs 0169 through 0173, pages 38-39.

Third, Applicant respectfully asserts that the Examiner has mischaracterized the teachings of both the Kuby and Abaza references. The Examiner contends that the Kuby reference teaches that "[i]mmunization with a peptide *fragment* derived from a full length polypeptide may result in antibody specificity that differs from the antibody specificity directed against the native *full-length* polypeptide." Office Action at page 4 (emphasis added). However, the Kuby reference actually discusses whether antibodies that are raised against *full length* polypeptides can bind *fragments* of the full length polypeptide. Thus, the teachings of the Kuby reference fail to support the Examiner's argument.

Similarly, the Abaza reference does not teach that antibodies raised against specific fragments of a polypeptide would not react with the full-length polypeptide. On the contrary, the reference discloses that antibodies generated from a 6 amino acid fragment of sperm whale myoglobin bound to the full length sperm whale myoglobin. *See* Abaza page 435. Thus, the Abaza reference also fails to support the Examiner's argument.

In addition, as suggested by Abaza, one of ordinary skill in the art would know that it was typical to use small peptide fragments to make antibodies to bind to the full length protein. The specification itself teaches that a sequence encoding only a fragment of the polypeptide can be used to generate antibodies capable of binding the whole native polypeptide. *See* specification at paragraph 0170, page 38. Finally, the Examiner is respectfully requested to note that the claims have been amended to recite "producing" an antibody instead of "binding" an antibody.

Therefore, since the disclosed or otherwise known methods of making and screening the claimed polypeptide fragments may be used to determine, without undue

experimentation, whether a given polypeptide fragment encompassed by the claim can be used to (a) produce an antibody specific to the polypeptide of SEQ ID NO:2, (b) induce apoptosis of a cell line derived from pathologic tissue or (c) induce apoptosis of T cells, the enablement requirement is fully satisfied. *In re Wands*, 858 F.2d at 738, 8 U.S.P.Q.2d at 1404; *Ex parte Mark*, 12 U.S.P.Q.2d 1904, 1906-1907 (B.P.A.I. 1989).

With regard to claim 25, subparts (c)-(f) and (h), the Examiner has alleged that "there is insufficient guidance as to the structure of the nucleic acid encoding which undisclosed amino acid wherein the polynucleotide encoding amino acids 1 to 281 of SEQ ID NO:2 or 39-291 of SEQ ID NO:2 having 1 to 5 or 5 to 10 conservative amino acid substitution." Office Action at page 6. The Examiner has also alleged that "there is insufficient guidance as to the structure of the nucleic acid encoding which undisclosed protein wherein the polynucleotide is complementary to 'which polynucleotide that hybridizes to' the nucleotide encoding amino acids 1 to 281. . . or 39 to 281 of SEQ ID NO:2 or nucleotide encoding the amino acid sequence encoded by the human cDNA contained in ATCC Deposit No. 97448. . . ." Office Action at page 6. Applicant respectfully disagrees with this rejection. However, to expedite prosecution of the present application and not in acquiescence to this rejection, Applicant has amended claim 25 to remove subparts (c)-(f), and (h).

With regard to claims 12 and 27, the Examiner has alleged that "there is inadequate teaching and *in vivo* working example how to use the undisclosed polypeptide for treating **all** disease such as autoimmune disease, graft versus host disease and tumor. . . . [T]here is a lack of *in vivo* working example demonstrating that the claimed composition could treat **all** disease." Office Action at pages 6-7 (emphasis added). Applicant respectfully disagrees. First, the specification does not assert that the

polypeptides could treat **all** diseases. Second, as indicated above, there is both ample guidance in the specification and it is well known in the art how to make the claimed polypeptides. Third, the specification clearly contemplates that the claimed polypeptides can be employed in a composition with a pharmaceutically acceptable carrier. *See* specification at paragraphs 0174 through 0176, page 39.

Furthermore, according to the MPEP:

> when a compound or composition claim is not limited by a recited use, **any enabled use** that would reasonably correlate with the entire scope of that claim is sufficient to preclude a rejection for non-enablement based on how to use. If multiple uses for claimed compounds or compositions are disclosed in the application, then an enablement rejection must include an explanation, sufficiently supported by the evidence, why the specification fails to enable each disclosed use. In other words, if any use is enabled when multiple uses are disclosed, the application is enabling for the claimed invention.

See MPEP 2164.01(c) (emphasis added). Therefore, given that claims 12 and 27 are composition claims, the Applicant is only required to show one utility.

In the present case, the specification clearly discloses how AIM-I polypeptide can be used to treat certain diseases, such as cancer:

> The AIM-I of the present invention may also be employed to inhibit neoplasia, such as tumor cell growth. The AIM-I polypeptide may be responsible for tumor destruction through apoptosis and cytotoxity to certain cells.

Specification at paragraphs 0174-0175, page 39. Therefore, one of ordinary skill in the art would know how to use the claimed compositions without undue experimentation.

In addition, the Examiner is reminded that:

> a specification disclosure which contains a teaching of the manner and process of making and using the invention . . .

> must be taken as in compliance with the enabling requirement of the first paragraph of § 112 unless there is a reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support.

In re Marzocchi, 439 F.2d 220, 223 (CCPA 1971). Given that the Examiner has not given any reasons or evidence that one of skill in the art could not use the claimed compositions for any of the disclosed or well-established pharmaceutical uses, Applicant respectfully asserts that the Examiner has failed to meet this required burden.

The Examiner further alleges that there is "a lack of *in vivo* working example demonstrating that the claimed composition could treat all disease." Office Action at page 7. However, the Examiner is reminded the Federal Circuit in *In re Brana*, 34 U.S.P.Q. 2d 1436 (1995) specifically pointed out that

> [u]sefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful is well before it is ready to be administered to humans.

Furthermore, there is no statutory requirement for a specific working example of a claim - a patent specification is not intended nor required to be a production specification. *In re Gay*, 309 F. 2d 768, 135 USPQ 311 (CCPA 1962); *see* M.P.E.P. 2165.01. The current specification clearly teaches the production of polypeptides and fragments thereof and any one skilled in the art would be able to use the claimed compositions for both the disclosed and well-established pharmaceutical uses for the claimed proteins.

Thus, Applicant respectfully asserts that one of ordinary skill in the art would be able to make and use the invention, as presently claimed, without undue experimentation. Accordingly, reconsideration and withdrawal of the rejection under 35 U.S.C. § 112, first paragraph, are respectfully requested.

B. The Written Description Rejection Of Claims 1-12, 16, and 18-29

In section 6 of the Office Action at page 7, the Examiner has rejected claims 1-12, 16, and 18-29 under 35 U.S.C. § 112, first paragraph for allegedly "containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention." Office Action at page 7. Applicant respectfully disagrees with this rejection. However, as indicated above, claims 1-7, 11, 16, 18-24, 26 and 28-29 have been cancelled without prejudice or disclaimer, thus rendering moot the portion of this rejection that applied to these claims. Furthermore, claims 8-10 and 25 have been amended, thus rendering moot the portion of this rejection that applied to these claims. Applicant respectfully traverses this rejection, as it may be applied to the remaining claims.

In an analysis of written description under 35 U.S.C. § 112, first paragraph, the Examiner bears the initial burden of presenting a *prima facie* case of unpatentability. This burden is only discharged if the Examiner can present evidence or reasons why one skilled in the art would not reasonably conclude that Applicants possessed the subject matter as of the priority date of the present application. *In re Wertheim*, 541 F.2d 257, 262, 191 U.S.P.Q.2d 90, 96 (C.C.P.A. 1976); M.P.E.P. § 2163.04. In the instant case, Applicant maintains that the Examiner has not met this burden.

The test for the written description requirement is whether one skilled in the art could reasonably conclude that the inventor had possession of the claimed invention based on the specification as filed. *Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1563, 19 U.S.P.Q.2d 1111, 1116 (Fed. Cir. 1991); M.P.E.P. § 2163.02. Indeed, as the Federal

Circuit has noted, "the issue is whether one of skill in the art could derive the claimed ranges from the patent's disclosure." *Union Oil Company of California v. Atlantic Richfield Company*, 208 F.3d 989, 54 U.S.P.Q. 2d 1227 (Fed. Cir. 2000) (emphasis added).

The AIM-I polypeptide is a member of the TNF-ligand superfamily. It was well known in the art that there was a characteristic pattern of sequence conservation in the TNF family ligands. *See, e.g.*, Gruss and Dower, *Blood 85*:3378-3404 (1995) (Exhibit A). Given that the skilled artisan would have been familiar with this well known conservation among TNF family ligands and given the teachings of the present application, the skilled artisan could clearly envision the fragments that would retain the structural and/or functional attributes of AIM-I. Thus, it would be readily apparent to the skilled artisan that the Applicant had "invented what is claimed" *Vas-Cath*, 935 F.2d at 1563. Accordingly, one skilled in the art, enlightened by the teachings of the present application, could readily envision all of the various polypeptide sequences of the specified polypeptides.

With regard to claim 8 and 9, the Examiner alleged that "there is inadequate written description about which continguous 30 or 50 amino acids of SEQ ID NO:2 binds an antibody that is specific to the polypeptide of SEQ ID NO:2 and which contiguous 30 or 50 amino acids of SEQ ID NO:2 induces apoptosis in T cells or cell derived from which pathological tissue." Office Action at page 8. Applicant respectfully disagrees. First, based on the well-characterized sequence conservation within the TNF ligand family, one of skill in the art could recognize and clearly envision sequences of SEQ ID NO:2 that would have apoptotic activity. *See* Exhibit A. Furthermore, most if not all of the claimed stretches of the polypeptide could produce an antibody that would

bind the full-length protein. Nevertheless, to expedite prosecution of the application, and not in acquiescence to this rejection, claims 8 and 9 have been amended to remove the functional language.

With regard to claim 10 and 12, the Examiner has alleged that "there is inadequate written description about which fragment of amino acids of SEQ ID NO:2 binds an antibody specific to the polypeptide of SEQ ID NO:2, or induces apoptosis in T cells or cell line derived from all pathological tissue. Further, the term 'comprising is open-ended. It expands the fragment to include additional amino acids at either or both ends." Office Action at page 8. Applicant respectfully disagrees. First, based on the well-characterized sequence conservation within the TNF ligand family, one of skill in the art could recognize and clearly envision sequences of SEQ ID NO:2 that would have apoptotic activity. *See* Exhibit A. Furthermore, most if not all of the claimed stretches of the polypeptide could produce an antibody that would bind the full-length protein. Nevertheless, to expedite prosecution, and not in acquiescence to this rejection, Applicant has amended claim 10 to recite "consisting of."

Applicant asserts that the specification conveys with reasonable clarity that the Applicant was in possession of the claimed invention and that the claims are fully supported by the specification. Moreover, Applicant respectfully asserts that the Examiner has failed to meet the required burden in presenting evidence or reasons why those skilled in the art would not recognize the claimed invention from the disclosure. For all of the above reasons, Applicant respectfully asserts that the present specification provides sufficient written description to convey to one of ordinary skill that Applicant had possession of the full scope of the claimed invention upon filing of the application.

Accordingly, reconsideration and withdrawal of the rejection under 35 U.S.C. § 112, first paragraph, are respectfully requested.

C. The New Matter Rejection Of Claims 1-12 and 18-29

In section 7 of the Office Action at page 10, the Examiner has rejected claims 1-12 and 18-29 for allegedly introducing new matter into the claims. Applicant respectfully disagrees with this rejection. However, to expedite prosecution of the present application and not in acquiescence to this rejection, Applicant has amended the claims to recite "producing" instead of "binding." Support for this amendment can be found in the specification, for example, at paragraph 0169, page 38 through 0173, page 39. Accordingly, reconsideration and withdrawal are respectfully requested.

IV. The Rejection Under 35 U.S.C. § 112, Second Paragraph

In section 9 of the Office Action at page 10, the Examiner has rejected claims 18, 21, and 22 for allegedly being indefinite for failing to point out and distinctly claim the subject matter which Applicant regards as the invention. As indicated above, claims 18, 21 and 22 had been cancelled without prejudice or disclaimer, thus rendering moot the portion of this rejection that applied to these claims.

V. Entitlement to Priority

In section 10 of the Office Action at page 10, the Examiner has alleged that

> the filing date of the instant claims 1-12, and 18-29 is deemed to be the filing date of the instant application 9/16/03, as the provisional 60/013,405 is drawn only to a purified protein comprising a polypeptide sequence selected from the group consisting of (a) the amino acid sequence of the full-length polypeptide encoded by the human cDNA contained in ATCC Deposit No. 97448 and

> (b) the amino acid sequence of the mature polypeptide encoded by the human cDNA contained in ATCC Deposit No. 97448 . . ., and thus does not support the claimed limitation "binding an antibody specific to the polypeptide of SEQ ID NO:2. . . ."

Office Action at pages 10-11.

As indicated above, Applicant has amended the claims to recite "producing" instead of "binding." Furthermore, Applicant respectfully points out that the specification in the present application filed on September 16, 2003 is substantively identical to the specification filed in the U.S. Provisional Application 60/013,405 (the '405 application) on March 14, 1996. Four differences in formalities may be noted: (a) the priority claim; (b) the assignment of SEQ ID NOs. to sequences which were already disclosed; (c) the General Information section of the Sequence Listing; and (d) paragraph numbering. A copy of the '405 application is being provided to the Examiner as Exhibit C. Therefore, given that the disclosures of the instant application and the U.S. Provisional Application 60/013,405 are substantively identical, the instant application has priority back to the March 14, 1996 filing date of the '405 application.

VI. The Rejections Under 35 U.S.C. § 102

A. The 35 U.S.C. § 102(b) Rejection Over U.S. Patent No. 6,030,945

In section 13 of the Office Action at page 11, the Examiner has rejected claims 1-12 and 18-29 under 35 U.S.C. § 102(b) as allegedly being anticipated by U.S. Patent No. 6,030,945 (hereinafter "the '945 patent"). Applicant respectfully traverses this rejection.

The '945 patent specification became public no earlier than February 24, 2000. Since the instant application, as indicated above, claims priority under 35 U.S.C. § 119(e), back to the March 14, 1996 filing date of the '405 application, the '945 patent is

not a proper 102(b) reference. Accordingly, Applicant requests that the Examiner reconsider and withdraw the rejection under 35 U.S.C. § 102(b).

B. The 35 U.S.C. § 102(b) Rejection Over U.S. Patent No. 5,763,223

In section 14 of the Office Action at page 12, the Examiner has rejected claims 1-12 and 18-29 under 35 U.S.C. § 102(b) as allegedly being anticipated by U.S. Patent No. 5,763,223 (hereinafter "the '223 patent"). Applicant respectfully traverses this rejection.

The '223 patent specification became public no earlier than June 9, 1998. Since the instant application, as indicated above, claims priority under 35 U.S.C. § 119(e), back to the March 14, 1996 filing date of the '405 application, the '223 patent is not a proper 102(b) reference. Accordingly, Applicant requests that the Examiner reconsider and withdraw the rejection under 35 U.S.C. § 102(b).

C. The 35 U.S.C. § 102(b) Rejection Over Wiley

In section 15 of the Office Action at page 12, the Examiner has rejected claims 1, 4, 6, 8-17 and 25-28 under 35 U.S.C. § 102(b) as allegedly being anticipated by Wiley *et al* (*Immunity* 3:673-682 (1995) (hereinafter "Wiley")). Applicant respectfully traverses this rejection.

According to the Examiner, Wiley was first made public in December of 1995. Since the instant application, as indicated above, has priority back to the March 14, 1996 filing date of the '405 application, the Wiley literature reference, appearing less than one year prior to March 14, 1996, is not a proper 102(b) reference. Accordingly, Applicant requests that the Examiner reconsider and withdraw the rejection under 35 U.S.C. § 102(b).

D. The 35 U.S.C. § 102(e) Rejections Over U.S. Patent No. 6,030,945 and U.S. Patent No. 5,763,223

In section 16 and 17 of the Office Action at pages 15 and 16, the Examiner has rejected claims 1-29 under 35 U.S.C. § 102(e) as allegedly being anticipated by the '945 patent and the '223 patent, respectively. Applicant respectfully traverses this rejection.

The earliest claims to priority for the '945 and '223 patents are January 9, 1996 and June 29, 1995, respectively.[1] A showing under 37 C.F.R. § 41.202(d), demonstrating priority over Wiley's U.S. Patent No. 6,284,236 ("the '236 patent"), is being filed concurrently herewith. The '223 patent is related to the '236 patent as follows. Wiley's '236 patent issued from Application No. 09/320,424, filed May 26, 1999, which is a continuation-in-part of Application No. 09/190,046, filed November 10, 1998, now abandoned, which is a continuation-in-part of Application No. 09/048,641, filed March 26, 1998, now abandoned, which is a continuation-in-part of Application No. 08/670,354, filed June 25, 1996, now U.S. Patent No. 5,763,223. Both patents claim priority to the same filing date, i.e., June 29, 1995. The attached 202(d) showing constitutes a complete reply in full compliance with the requirements of 37 C.F.R. § 1.111 and is responsive to all the 35 U.S.C. 102(e) rejections in this Office Action. Specifically, it is believed that the showing under 37 C.F.R. § 41.202(d) over Wiley's U.S. Patent No. 6,284,236 establishes conception prior to the earliest claimed priority dates of the '945 and '223 patents coupled with diligence from just prior to the June 29, 1995 earliest claimed priority date of the '223 patent and '236 patents to Applicant's constructive reduction to practice on March 14, 1996. Accordingly, it is believed that

[1] The '223 patent is 2 CIP's removed from June 29, 1995 so the effective filing date of the relevant subject matter of the '223 patent may be later.

this showing fulfills the requirements of a declaration of prior invention under 37 C.F.R. § 1.131 sufficient to antedate the disclosures of both U.S. Patent No. 6,030,945 and U.S. Patent No. 5,763,223. Thus, reconsideration and withdrawal of these rejections are respectfully requested.

V. Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicant therefore respectfully requests that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicant believes that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.

Elizabeth J. Haanes, Ph.D.
Attorney for Applicant
Registration No. 42,613

Date: April 1, 2005

1100 New York Avenue, N.W.
Washington, D.C. 20005-3934
(202) 371-2600

Exhibit A Gruss and Dower, *Blood 85*:3378-3404 (June 15, 1995).

Exhibit B Suda *et al.*, *Cell 75*:1169-1178 (1993).

Exhibit C Ruben Provisional Application 60/013,405, filed March 14, 1996

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